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DANN, DORFMAN, HERRELL & SKILLMAN 1601 MARKET STREET SUITE 2400 PHILADELPHIA, PA 19103-2307			KERR, KATHLEEN M	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 09/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/720,840

Applicant(s)

LEADLAY ET AL.

Examiner

Kathleen M Kerr

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 June 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 54-76 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 54-76 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (mailed on December 16, 2003), Applicants filed an amendment and response received on June 21, 2004. Said amendment cancelled Claims 20, 23-25, 29, 30, and 43-53, amended Claims 54-56, and 60-63, and added new Claims 64-76. Thus, Claims 54-76 are pending in the instant Office action and will be examined herein.

Priority

2. As previously noted, the instant application is granted the benefit of priority for International Application No. PCT/GB99/02044 filed on June 29, 1999 and UK Application No. 9814066.4 filed on June 29, 1998.

Withdrawn - Objections to the Specification

3. Previous objection to the specification for its description of the figures is withdrawn by virtue of Applicant's amendment.

Withdrawn – Claim Objections

4. Previous objection to Claims 43, 46, and 54 for a typographical error is withdrawn by virtue of Applicant's amendment and/or cancellation of said claims.

Withdrawn - Claim Rejections - 35 U.S.C. § 112, second paragraph

5. Previous rejection of Claims 20, 23-25, 29, 30, and 43-63 under 35 U.S.C. § 112, second paragraph, as being indefinite because the independent “base” claims are generally narrative and indefinite, is withdrawn by virtue of Applicant’s amendment to Claim 54 as well as having Claims 64, and 72-76, all “base” claims, all follow the form proposed by the Examiner.

6. Previous rejection of Claims 20, 23-25, 29, 30, and 43-63 under 35 U.S.C. § 112, second paragraph, as being indefinite for the use of the term “residue” is withdrawn by virtue of Applicant’s amendment to the term ---moiety--- as suggested by the Examiner.

7. Previous rejection of Claims 20, 23-25, 30, and 43-53 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase “corresponding to” (referring to the natural KSq) is withdrawn by virtue of Applicant’s cancellation of said claims.

8. Previous rejection of Claims 20, 23-25, 30, and 43-53 under 35 U.S.C. § 112, second paragraph, as being indefinite for the nature of “a cysteine in the active site” is withdrawn by virtue of Applicant’s cancellation of said claims.

9. Previous rejection of Claims 20, 23-25, and 55-56 under 35 U.S.C. § 112, second paragraph, as being indefinite for the antecedent basis of “the acyltransferase domain” (AT) is withdrawn by virtue of Applicant’s amendment to ---said acyltransferase domain--- as suggested by the Examiner.

10. Previous rejection of Claims 46-53 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term “derived from” is withdrawn by virtue of Applicant’s cancellation of said claims.

11. Previous rejection of Claims 50-51 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase “corresponds to” is withdrawn by virtue of Applicant’s cancellation of said claims.

Maintained - Claim Rejections - 35 U.S.C. § 112, second paragraph

12. Previous rejection of Claims 54-63 under 35 U.S.C. § 112, second paragraph, as being indefinite for the nature of the loading module is maintained. Moreover, new Claims 64-76 are rejected herein for the same reasons (the phrase “at least the first of said extension modules is not naturally associated with said loading module”) as follows. Applicant’s arguments have been fully considered but are not deemed persuasive for the following reasons. As noted by Applicant, “Applicants respectfully take exception to the Examiner’s contention that ‘virtually all loading modules in nature ... effect decarboxylation of an optionally substituted malonyl.’ Indeed ... skilled artisans were not aware that loading modules that did contain a KSq domain had the recited functionally.” The Examiner maintains her “contention” because regardless of what the skilled artisan knew at the time of the invention about the functionality of KSq domains, the fact remains that KSq domains inherently do this and the mere possession of KSq domains, regardless of an understanding of their functionality, anticipates the claim limitation.

Applicant also argues “the claims, as amended, plainly refer to the loading module **as a unit** and should not be naturally associated with at least the first of the extension modules”

(emphasis added). The Examiner fails to find this limitation in the claims and does not understand what “unit” is intended. Clearly, the claims are meant to encompass loading modules having KS, AT, and ACP domains from different sources. For example, Claim 60 requires the use of an extension module’s AT domain in the loading module of the claimed PKS; therefore, this loading module could not possible exist “as a unit” in nature. Such limitations are also found in Claims 56, 57, 61-69, and 73. Therefore, since the loading module is not considered “as a unit” but can be considered as its parts (KS, AT, and ACP), it must be clear what the extension modules must not be naturally associated with. Just the ACP since this is the 3’ unit of the loading module? Or just the KS? Or all three units? Clarification is required.

Withdrawn - Claim Rejections - 35 U.S.C. § 112, first paragraph

13. Previous rejection of Claims 25, 49, and 60 under 35 U.S.C. § 112, first paragraph, new matter, is withdrawn by virtue of Applicant’s amendment removing reference to using *any* acyltransferase domain as opposed to the specific AT5 of monensin or spiramycin.

14. Previous rejection of Claims 30, 53, and 63 under 35 U.S.C. § 112, first paragraph, new matter, is withdrawn by virtue of Applicant’s amendment removing the limitation of a PKS that produces a polyketide having a side chain of an allyl or hydroxymethyl group and replacing it with use of AT4 of FK506 or AT6 of niddamycin.

15. Previous rejection of Claims 20, 23-25, 29, 30, 43, 44, 53, and 63 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by virtue of Applicant’s cancellation and/or Applicant’s arguments. Applicant argues that the use of methymycin in the specification

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supports the genus of 12-membered macrolides that start with either acetate or propionate. This is found persuasive based on the totality of the specification.

The Examiner notes that the claim requires the following:

- (a) 12-membered macrolides that start with acetate (malonyl-specific)
- (b) 12-, 14-, and 16-membered macrolides that start with propionate (methylmalonyl-specific).

Methymycin (12-membered) starts with propionate, i.e., describing item (b) but not describing item (a); however, a hybrid PKS using the extension modules of methymycin with a malonyl-specific (acetate) loading module would describe item (a). The rejection is withdrawn.

16. Previous rejection of Claims 20, 23-25, 30, and 43-63 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by virtue of Applicant's cancellation and/or amendment to remove the word "adapted" from the claim as it referred to AT domains.

Maintained - Claim Rejections - 35 U.S.C. § 112, first paragraph

17. Previous rejection of Claims 54-63 under 35 U.S.C. § 112, first paragraph, written description, is maintained. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicant argues that the engineering of a known KSq domain, such as taking a KS domain from an extension module and mutating the active site Cys to a Gln, is described; the Examiner does not disagree. However, the instant claims are not limited to this product-by-process type language wherein a naturally occurring KS domain would be used (a KS domain

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that contained the requisite active site Cys residue), whether from a loading module or an extension module, and mutated into a KSq domain.

By the word “engineered”, the instant claims exclude KSq domains that naturally occur, such as that of tylosin, which is used in a hybrid PKS taught by Kuhstoss *et al.* The specification does not describe the structure of the genus of hybrid PKSs with KSq domains that are engineered (see above) to the exclusion of hybrid PKSs with KSq domains that naturally occur. In other words, no description of how an engineered KSq domain is different from a naturally occurring KSq domain is found in the specification so that one of skill in the art would have understood that Applicant was in possession of the claimed invention to the full extent of its claimed “structure”.

Withdrawn - Claim Rejections - 35 U.S.C. § 102

18. Previous rejection of Claims 46, 48, 52, and 53 under 35 U.S.C. § 102(b) as being anticipated by Kuhstoss *et al.* is withdrawn by virtue of Applicant’s cancellation of said claims.

Withdrawn - Claim Rejections - 35 U.S.C. § 103

19. Previous rejection of Claims 20, 23-25, 29, 30, and 43 under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,712,146) in view of Khosla (Chemical Reviews (1997) 97:2577-2590) is withdrawn by virtue of Applicant’s cancellation of said claims.

20. Previous rejection of Claims 20, 23-25, 29, 30, 43-45, 47, and 49 under 35 U.S.C. 103(a) as being unpatentable over Khosla *et al.* (USPN 5,712,146) in view of Khosla (Harnessing the

Biosynthetic Potential of Modular Polyketide Synthases. Chemical Reviews (1997) 97:2577-2590) is withdrawn by virtue of Applicant's cancellation of said claims.

NEW ISSUES

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

21. Claim 63 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "wherein the starter unit is derived from a loading domain" is unclear. Must the starter unit be a part of the loading domain? These are amino acid sequences, while polyketides and their starter units are acetate and propionate. Clarification is required.
22. Claims 73-76 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Items a and b extensively describe the structure/function of the loading module of the hybrid PKS. Then item (d) specifies a particular loading module from the art. It is unclear if all monensin, oleandomycin, tylosin, and spiramycin loading modules have the prescribed functions or if some subset of these modules is required. The inclusion of inherent functional language is confusing. Clarification is required.

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The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

23. Claims 64, 67 and 71 are rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to hybrid PKSs having a loading module comprising a KSq domain (any KS domain with a Q, not a C, in the active site), an AT domain that is AT2 of rapamycin, and an ACP domain. Such a genus is not supported in the specification as originally filed. Applicant must cite clear support (page and line number) for the alleged new matter or delete it.

In Applicant's remarks filed June 21, 2004, support for Claim 64 is cited as being found on page 47, in Example 11 (the other citation on page 27 does not describe AT2 of rapamycin). This example teaches a loading module of (1) a naturally occurring KSq from oleandomycin PKS, (2) an AT2 from rapamycin PKS and (3) an ACP from the DEBS loading module. Therefore, this example cannot support claims wherein the KSq domain can be any KSq domain. This example does support the AT2-of-rapamycin-PKS species of Claim 70.

24. Claims 70 and 72 are rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

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in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to hybrid PKSs having a loading module comprising a KSq domain that is of the loading module of oleandomycin PKS, an AT domain that is either limited by Claim 64 (for Claim 70) or not at all (for Claim 72), and an ACP domain. Such a genus is not supported in the specification as originally filed. Applicant must cite clear support (page and line number) for the alleged new matter or delete it.

In Applicant's remarks filed June 21, 2004, support for Claims 70 and 72 is cited as being found on page 47, in Example 11 (the other citation on page 27 does not describe the oleandomycin loading module). This example teaches a loading module of (1) a naturally occurring KSq from oleandomycin PKS, (2) an AT2 from rapamycin PKS and (3) an ACP of the DEBS loading module. Therefore, this example cannot support claims to a hybrid PKS having the KSq from oleandomycin PKS wherein the AT is any AT or the specific ones in Claim 64 (except for AT2 from rapamycin PKS).

The Examiner notes that on page 21 of the specification, use of loading modules of oleandomycin are envisioned (Claim 74 is supported); however, this disclosure is not specific for using the KSq domain of the oleandomycin PKS but for using the loading module of oleandomycin *as a whole*. Pages 21-22 support this aspect of Claims 73-76 using the loading modules, *as whole entities*, of the PKSs of monensin, oleandomycin, tylosin, or spiramycin.

25. Claim 75 is rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the

claimed invention. The instant claim is drawn to hybrid PKSs having a tylosin loading module and a plurality of extension modules wherein a 12- or 14-membered macrolide is produced. Such a sub-genus is not supported in the specification as originally filed. Applicant must cite clear support (page and line number) for the alleged new matter or delete it.

In Applicant's remarks filed June 21, 2004, support for Claim 75 is cited as being found on page 22 (Claim 43 is not "original" and cannot be used to support the amendment). Page 22 generically supports using the tylosin loading module, combined with extension modules, to produce polyketides. No description of the sub-genus wherein only 12- and 14-membered polyketides is described. Such an added limitation seems to be in direct response to an anticipated art rejection citing Kuhstoss *et al.*, who teach using the tylosin loading module with spiramycin extension modules to produce a 16-membered polyketide (see previous art rejection of record), and not in possession of the inventors at the time of filing.

26. Claims 60, 64, and 69-71 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Although the genus of hybrid PKSs comprising an AT5 from a monensin PKS gene cluster as the acyltransferase of its loading module is discussed in the specification, there is no evidence that any representative species was in the possession of the inventors at the time of filing.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics,

functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. Unlike for spiramycin PKS, the prior art does not teach the PKS gene cluster for monensin. While the concept of an AT5 from the monensin PKS gene cluster, which at the time of the invention was hypothetical, is envisioned, no representative species is disclosed, with or without identifying characteristics. Therefore, Claims 60, 64, and 69-71 fail to satisfy the written description requirement.

27. Claims 70, 72 and 74 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Although the genus of hybrid PKSs comprising either just the KSq of an oleandomycin loading module or the entire oleandomycin loading module is discussed and, for the KSq alone, somewhat exemplified in the specification, the description of such is inadequate to support the claimed invention.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. Unlike for loading modules having KSq domains of known PKS gene clusters at the time of the invention, the prior art does not teach the PKS gene cluster for oleandomycin. On page 49 of the instant specification, description of obtaining and using a KSq

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domain from *S. antibioticus* (for oleandomycin) is taught; however, a complete description of the KSq domain is wholly lacking in the absence of DNA sequence and/or more specific experimental conditions for the example. Thus, this teaching cannot support the genus of KSq domains from oleandomycin PKS. Additionally, while the concept of a complete loading module (not just the KSq) from the oleandomycin PKS gene cluster, which at the time of the invention was hypothetical, is envisioned, no representative species is disclosed, with or without identifying characteristics. Therefore, Claims 70, 72 and 74 fail to satisfy the written description requirement.

28. Claim 71 is rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Although the genus of hybrid PKSs comprising the extension modules of immunomycin (FK-520) PKS is discussed in the specification, the description of such is inadequate to support the claimed invention.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. Unlike for extension modules of known PKS gene clusters at the time of the invention (like rifamycin, avermectin, and rapamycin), the prior art does not teach the PKS gene cluster for immunomycin (FK-520). While the concept of extension modules from the

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immunomycin PKS gene cluster, which at the time of the invention was hypothetical, is envisioned, no representative species is disclosed, with or without identifying characteristics.

Therefore, Claim 71 fails to satisfy the written description requirement.

29. Claim 73 is rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Although the genus of hybrid PKSs comprising the monensin loading module is discussed and somewhat exemplified in the specification, the description of such is inadequate to support the claimed invention.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. Unlike for loading modules having KSq domains of known PKS gene clusters at the time of the invention, the prior art does not teach the PKS gene cluster for monensin. On page 70 of the instant specification, description of obtaining and using an unclear portion of the loading module from *S. cinnamonensis* (for monensin) is found; however, a complete description of the loading module is wholly lacking in the absence of DNA sequence and/or more specific experimental conditions. Thus, this teaching cannot support the genus of the loading module for monensin PKS. Therefore, Claim 73 fails to satisfy the written description requirement.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

30. Claim 76 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kuhstoss *et al.* (see PTO-892 from previous Office action) in view of Khosla *et al.* (USPN 5,672,491). The instant claims are drawn to hybrid PKSs that are a combination of a spiramycin loading module with tylosin extension modules.

Kuhstoss *et al.* teach a hybrid polyketide synthase comprised of the tylosin loading module (KS^Q-AT-ACP) and the spiramycin extension modules (see page 233, left column and Figure 3). Kuhstoss *et al.* teach that the spiramycin loading module, just like the tylosin loading module used in the hybrid, has a KS^Q domain (see page 234, right column). This loading module of the spiramycin PKS *inherently* has the capacity for loading and decarboxylation as required in the instant claim. The spiramycin loading module and tylosin extension modules are not naturally associated with each other. Kuhstoss *et al.* also teach that the organization of PKS genes corresponds to the synthesis of the polyketide (see page 233, left column) such that a 16-membered macrolide is produced by the hybrid PKS. Kuhstoss *et al.* do not teach the “reverse” hybrid PKS wherein it is the spiramycin loading module with the tylosin extension modules as required for the instant claim.

Khosla *et al.* teach the production of hybrid type I PKS enzymes wherein the hybrids encompass domains and modules from type I PKSs such as tylosin, spiramycin, and monensin

(see column 12, lines 34-42). Khosla *et al.* also teach that the production of polyketides from type I PKSs has a “one-to-one correlation between the number and clustering of active sites in the primary sequence of the PKS and the structure of the polyketide backbone” (see column 2, lines 1-4).

At the time of the invention, it would have been obvious to use the teachings of Kuhstoss *et al.* to produce a hybrid PKS having the spiramycin loading module and the tylosin extension modules because Kuhstoss *et al.* produce the “reverse” hybrid PKS and teach the general applicability of their method “to generate lactone rings with their carbon skeletons modified at different condensation steps” (see page 235, left column). Since the tylosin loading module, and not the spiramycin loading module, was chosen as the loading module of the hybrid for no noted reason, the “reverse” hybrid is an obvious choice to reiterate the experiment and prove its general applicability. One would have been motivated to produce a hybrid PKS having the spiramycin loading module and the tylosin extension modules because of the usefulness of such a hybrid PKS to produce novel polyketides, which are therapeutically useful (see Khosla *et al.*). One would have had a reasonable expectation of success that (1) such a hybrid could be made based on the high expertise for DNA manipulation and expression in the art at the time of the invention and (2) such a hybrid would produce a 16-membered polyketide based on the understanding in the art, which is noted in both Kuhstoss *et al.* and Khosla *et al.*, that there is a one-to-one correlation between the structure of the PKS and the polyketide backbone it produces.

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Art Of Record

31. The following are noted by the Examiner:

- a) Oliynyk *et al.* (Chem. Biol. (1996) 10: 833-839) teaches swapping the first AT (of the loading module) in a DEBS PKS (DEBS1-TE, which is a truncated erythromycin PKS) with AT2 from rapamycin. Oliynyk *et al.* do not teach such swapping using a loading module with a KSq domain.

Summary of Pending Issues

32. The following is a summary of the issues pending in the instant application; each issue must be addressed in a complete response to the instant Office action:

- a) Claims 54-76 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the nature of the loading module.
- b) Claim 63 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase “wherein the starter unit is derived from a loading domain”.
- c) Claims 73-76 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for including inherent functionality in the claims.
- d) Claims 64, 67 and 71 stand rejected under 35 U.S.C. § 112, first paragraph, new matter (any KSq domain with AT2 of the rapamycin PKS).
- e) Claims 70 and 72 stand rejected under 35 U.S.C. § 112, first paragraph, new matter (KSq domain of oleandomycin PKS with any AT).
- f) Claim 75 stands rejected under 35 U.S.C. § 112, first paragraph, new matter (tylosin loading module only producing 12- or 14-membered macrolides).
- g) Claims 54-63 stand rejected under 35 U.S.C. § 112, first paragraph, written description, for the engineered KSq domain.
- h) Claims 60, 64, and 69-71 stand rejected under 35 U.S.C. § 112, first paragraph, written description (monensin AT5, no example).
- i) Claims 70, 72 and 74 stand rejected under 35 U.S.C. § 112, first paragraph, written description (KSq or entire loading domain of oleandomycin PKS, inadequately described example or no example).
- j) Claim 71 stands rejected under 35 U.S.C. § 112, first paragraph, written description (extension modules of immunomycin PKS, no example).
- k) Claim 73 stands rejected under 35 U.S.C. § 112, first paragraph, written description (monensin loading module, inadequately described example).
- l) Claim 76 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Kuhstoss *et al.* in view of Khosla *et al.* (USPN 5,672,491).

Conclusion

33. No claims are allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Kathleen M Kerr
Primary Examiner
Art Unit 1652

September 15, 2004